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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/125,751	10/30/98	FODSTAD	0 4885.55USWO

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EXAMINER	
UNGAR,S	
ART UNIT	**PAPER NUMBER**
1642	16

DATE MAILED: 10/25/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/125,751	Fodstad et al
Examiner	**Group Art Unit**
Ungar	1642

☒ Responsive to communication(s) filed on *Aug 14, 2000*.

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1, 3-6, 13, and 14* is/are pending in the application.

Of the above, claim(s) *13* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1, 3-6, and 14* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

1. The Amendment filed August 14, 2000 (Paper No. 15) in response to the Office Action of April 5, 2000 (Paper No 13) is acknowledged and has been entered. Previously pending claims 1, 3, 6 and 14 have been amended. Claims 1, 3, 6-8 and 14 are currently being examined.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The following rejections are being maintained:

Claim Rejections - 35 USC § 112

4. Claims 1, 3 and 6-8 remain rejected under 35 USC 112, first paragraph for the reasons previously set forth in Paper No. 13, Section 6, pages 3-6.

Applicant argues that (a) one skilled in the art would not have to perform undue experimentation to use the claimed invention because the *in vitro* results are the basis for *in vivo* use and because immunotoxin therapy was known in the art, (b) Applicant cites Pai et al to demonstrate that immunotoxins could cross react with normal cells and references to demonstrate that the general use of immunotoxins *in vivo* was known in the art and cites Kosterink et al to demonstrate that MOC 31 has been used for imaging, (c) combining the disclosed *in vitro* assays and the description of *in vivo* procedures and the learning from the prior art, a skilled person would know how to use the present method without undue experimentation, (d) in the claimed method CD-34+ cells are not selected *in vivo* they are cells of a population upon which immunotoxins can be used according to the claimed invention. The arguments have been considered but have not been found persuasive (a') for the reasons previously set forth drawn to the unpredictability of anticancer

drug discovery and differences between *in vitro* assays and complex conditions of *in vivo* therapy. Further, in the Unkun article submitted as Appendix 3C the authors clearly state that while immunotoxins have the potential for clinical use, many difficulties with immunotoxins remain. These difficulties include cross-reactivity with normal cells, demonstrated immune responses to antibody and toxin even in immunosuppressed patients and lack of potency in tolerated doses. In addition, Applicant's statement in the specification as originally filed that "due to the high specific activity of the disclosed immunotoxins *in vitro* **it seems possible** (emphasis added) to administer the mixture for *in vivo* treatment" clearly reflects the known unpredictability of anticancer drug discovery and the unpredictability of the claimed method in particular. No one of skill in the anticancer drug discovery art would believe the assertion that the invention would function as claimed based only on the disclosed *in vitro* assays and the hypothesized "possibility" that the mixture can be administered for *in vivo* treatment, (b') and (c') the cited references are not drawn to the claimed invention and it cannot be predicted that the invention will function as claimed based solely on the *in vitro* assays and generally taught *in vivo* procedures disclosed in the specification and the cited references for the reasons previously set forth, (d') the claims as written specifically claim an *in vivo* method wherein CD-34+ cells are selected from the nucleated cells in peripheral blood and since the dependent claims have all of the limitations of the claims from which they depend. This particular rejection could be obviated by amending the claims to separate the *in vivo* and *ex-vivo* limitations. Applicant's arguments have not been found persuasive and the rejection is maintained.

5. Claim 3 remains rejected under 35 USC 112, first paragraph for the reasons previously set forth in Paper No. 13, Section 7, pages 6-9.

Applicant argues that BM7 is available from S. Kaul whose address is provided in a cited reference and further, BM7 is cited in a copy of Investigational New Drug Application. The argument has been considered but has not been found persuasive. The antibody is not commercially available, there is no indication that the antibody is irrevocably available to the public without restriction and there is no indication that the antibody will be made available even if viable samples cannot be dispensed by S. Kaul.

Applicant argues that MOC31 is publically available from MCA Development b.v and submits Appendix 4 to support the assertion. The argument has been considered but has not been found persuasive because a review of Appendix 4 reveals a packing list drawn to project NRH01. There is nothing in the Appendix that reveals that the antibody is commercially available, there is no indication that the antibody is irrevocably available to the public without restriction and there is no indication that the antibody will be made available even if viable samples cannot be dispensed by MCA Development.

Applicant's arguments have not been found persuasive and the rejection is maintained.

6. Claims 1, 3, 6-8 and 14 remain rejected under 35 USC 112, second paragraph for the reasons previously set forth in Paper No. 13, Sections 8(c) and 8(G), pages 10 and 11.

As drawn to Section 8(C), Applicant argues that the claims have been amended to replace "fragments" with antigen binding antibody fragments and active toxin fragments. The argument has been considered but has not been found persuasive because a review of claim 1 reveals that the unmodified term "fragments thereof" is still recited in the claim.

As drawn to Section 8(G), Applicant argues that antibodies BM7 and MOC31 are readily and publicly available and thus the designations are not necessary . The argument has been considered but has not been found persuasive because antibodies BM7 and MOC31 do not appear to be publicly available without restriction for the reasons set forth above.

Applicant's arguments have not been found persuasive and the rejection is maintained.

Claim Rejections - 35 USC § 103

7. Claims 1 and 14 remain rejected under 35 USC 103 for the reasons previously set forth in Paper No. 13, Section 10, pages 12-15.

Applicant argues that (a) the claimed method requires the use of PE and Lemoli et al uses RIP , (b) the immunotoxin of Lemoli et al kills both tumor cells and normal cells and nothing in Lemoli et al suggests the claimed method, (c) Bjorn et al does not overcome the deficiencies and Bjorn et al disclose exclusively *in vitro* studies and there is no suggestion in the reference as to how the immunotoxins could be used *in vitro* with cell populations comprising non-target cells vulnerable to the toxin, (d) Brugger does not suggest how to kill malignant cells and does not teach or suggest a method whereby a toxin is used to kill relatively few target cells, (e) Parry

et al provides no guidance as to how to produce monoclonal antibodies to MUC1 with the high degree of specificity needed for the present claimed method, (f) the '254 Patent teaches a DNA sequence coding for antigen recognized by GA 733.1 antibody, it is not possible to simply replace an unspecific antibody disclosed in the '254 patent with the present antibodies and conjugate them to toxins.

The arguments have been considered but have not been found persuasive because (a')-(f') Applicant is arguing the reference individually without clearly addressing the combined teachings. It must be remembered that the references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references which made up the state of the art with regard to the claimed invention. Applicant's claimed invention fails to patentably distinguish over the state of the art represented by the cited references taken in combination. In re Young, 403 F.2d 754, 159 USPQ 725 (CCPA 1968); In re Keller 642 F.2d 413,208 USPQ 871 (CCPA 1981), (b') the immunotoxin of Lemoli et al kills tumor cells as claimed, (c') the instant invention is only exemplified in an *in vitro* environment and Applicant bases the enablement of the invention on *in vitro* data and the Bjorn et al reference was used solely to demonstrate that PE kills tumor cells *in vitro*, (d') Brugger clearly provides motivation for the invention of the combined references and was used solely to provide the motivation for the combination of the references, (e') Parry et al teach monoclonal antibodies to MUC-1 and further, Applicant is arguing limitations not recited in the claims as presently constituted, (f') the '254 patent teaches Mab

GA733 which binds to an antigen expressed by the GA733-2 gene as claimed. The antibody is clearly not unspecific.

Applicant has argued the reference individually without clearly addressing the combined teachings. It must be remembered that the references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references which made up the state of the art with regard to the claimed invention. Applicant's claimed invention fails to patentably distinguish over the state of the art represented by the cited references taken in combination. In re Young, 403 F.2d 754, 159 USPQ 725 (CCPA 1968); In re Keller 642 F.2d 413,208 USPQ 871 (CCPA 1981).

Applicant's arguments have not been found persuasive and the rejection is maintained.

New Grounds of Objection

Specification

8. The amendment filed August 14, 2000 is objected to under 35 U.S.C. § 132 because it introduces new matter into the specification. 35 U.S.C. § 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

The originally filed Table 4 discloses a column headed by 1.0 ug/ml which shows a 2.5 log cell kill. The specification on page 16 clearly refers to a 2.5 log cell kill which was achieved at 1.0 ug/ml. The amended Table 4 replaces the original 1.0 ug/ml with 0.1 ug/ml, retaining the 2.5 log cell kill. There is no support in the specification as originally filed for a 0.1 ug/ml with a 2.5 log cell kill.

Applicant is required to cancel the new matter in the response to this Office action.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

9. Claims 1, 3, 6-8 and 14 are rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation of active toxin fragments has no clear support in the specification and the claims as originally filed. A review of the specification revealed support for toxin fragments but not "active" toxin fragments. The subject matter claimed in claims 1, 3, 6-8 and 14 broadens the scope of the invention as originally disclosed in the specification.

10. Claims 1, 3, 6-8 and 14 are rejected under 35 USC 112, second paragraph because claim 1 recites the phrase "active toxin fragments". The claims are confusing because it is not clear what type of activity is being claimed.

11. All other objections and rejections recited in Paper No. 13 are withdrawn.

12. No claims allowed.

13. Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL.** See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF

THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1640.

Susan Ungar
Primary Patent Examiner
October 20, 2000